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(54) Title: PROMPT-RELEASE PHARMACEUTICAL COMPOSITIONS

(57) Abstract

The present invention is represented by a prompt-release pharmaceutical composition, suitable in particular for oral use, comprising:
 a) a plurality of nuclei having dimensions between 50 and 500 μm , selected among microcrystals of the active ingredient and microgranules containing at least one active ingredient and at least one pharmaceutically acceptable excipient; b) a lipidic coating comprising a lipidic material sprayed in the melted state onto the said nuclei, and optionally at least one hydrophilic additive; c) a vehicle comprising one or more pharmaceutically acceptable excipients. The coated micronuclei can form a suspension which can be reconstituted by the patient immediately before use by simply adding the suspending phase, or formed into tablets or solid aggregates.

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PROMPT-RELEASE PHARMACEUTICAL COMPOSITIONS

FIELD OF INVENTION

The present invention concerns a pharmaceutical composition which promptly releases the active principle, suitable in particular for oral administration. The

- 5 present composition comprises coated nuclei containing one or more active ingredients, which may be for instance used in the preparation of extemporaneous suspensions, as well as of tablets or solid aggregates.

Suspensions are heterogeneous systems in which the continuous phase (external phase) is liquid or semisolid, while the dispersed phase (internal phase) consists of 10 solid particles that are insoluble in the medium used. Pharmaceutical suspensions can be prepared during the industrial production phase (ready-to-use suspensions), or prepared by the patient at the time of use (extemporaneous suspensions).

The suspension is one of the most versatile of the various pharmaceutical forms that can be used for administration, since it is suitable for the creation of preparations for 15 oral, injectable, and dermatologic use.

The use of suspensions for the administration of active ingredients has been known for some time, and ready-to-use oral suspensions are usually preferred in everyday practice. This preference is due to the fact that the patient must simply agitate the bottle prior to use, since the continuous liquid phase is already present in the bottle.

20 To take an extemporaneous suspension, however, the patient must first redisperse the powdered drug in water.

Examples of ready-to-use suspensions already on the market are Bactrim (R), a syrup with antibacterial action, and Maalox (R), a suspension with antacid action used to treat epigastric pain.

25 The preparation of these administration forms in quantity, with consistent and repeatable standard characteristics, is normally influenced by a large number of variables, for example the density of the internal and external phases; the ratio of the phase volumes; the viscosity of the external phase; and the dimensions, degree of aggregation, and shape of the particles. The variability of these parameters therefore causes difficulties in resuspension, even after agitation at the time of use, and in 30 some cases can lead to inhomogeneity in the distribution of the active ingredient.

In addition, currently available suspensions can have certain limitations which make them poorly suitable for use. This occurs, for example, when problems exist with instability of the vehicle or palatability of the suspended form, when active

ingredients with unpleasant organoleptic characteristics are used, or when mutually incompatible active ingredients are present simultaneously in the same formulation.

To eliminate these drawbacks, measures have been known for some time which tend to mask the active ingredient, isolating it from the ingestion medium.

- 5 One of the measures most frequently used is that of microencapsulation, which however implies the use of solvents and of a process that is costly in industrial terms. Another drawback of masking performed by means of microencapsulation consists in the delaying action that the encapsulating substances can exert with regard to release of the active ingredient.
- 10 On the other hand, in some cases this delaying effect has been used specifically in order to obtain a modulation of the release of the drug according to predetermined profiles. For example, US Patent 5,296,236 describes microgranular controlled-release suspensions for oral use which have the peculiarity of gradually releasing various types of active ingredient over time, thus adapting them to the various
- 15 desired therapeutic conditions.

A delay in the release of the active ingredient may, however, not always be desirable or necessary for the administration of certain active ingredients such as, for example, analgesics, antipyretics, antitussives, and the like.

Another advantage of suspensions consists in their particular ease of swallowing (typical of liquids), especially when compared to solid pharmaceutical forms.

It is in fact known that, especially in pediatrics and in the elderly, and in particular categories of patients suffering from motor coordination impairment, such as stroke victims, it can be difficult to take tablets.

The need to respond to this kind of problem is illustrated by the continuing search for devices making it easy to break a tablet to produce a powder that can be dispersed in water.

For example, international patent applications WO 95/6427 and WO 95/6428 have recently described devices in the form of a syringe or superimposed cups, capable of allowing breakage of the tablet and subsequent resuspension thereof in water. Such devices have obvious limitations, however, for example in the presence of poorly palatable active ingredients, leaving aside the fact that very often the excipients of the tablets are not among those most suitable for promoting suspension of the crushed tablet.

A particular need is therefore felt not only for drugs that are easily available in suspended form, but also, when necessary, for the ability to mask taste.

A number of active ingredients have such palatability problems. It is well known, for example, that the bitter and metallic taste of acetaminophen, a very common

5 analgesic and antipyretic, makes it difficult to administer this drug by means of liquid formulations, especially in pediatrics. Other examples consist of naproxen, a well-known anti-inflammatory characterized by the fact that it leaves an intense burning sensation in the mouth and of ibuprofen; diltiazem, a cardiovascular drug with a strongly bitter taste; and moguisteine, a bitter-tasting antitussive with anesthetic properties.

10 In the case of diltiazem in particular, the product is also highly unstable in aqueous solution, and it is therefore very advantageous to have available an extemporaneous suspension that has good stability as well as a pleasant taste.

The need has also been felt for formulations which control the hygroscopicity of
15 certain substances. For example, it is known from the literature that potassium bicarbonate can be used to prevent osteoporosis and hypertension [New Engl. J. Med. 330, 1251, 1776 (1994), and US Patent 5,171,583]. However, since this salt has tolerability and hygroscopicity problems, the ability to have available a pharmaceutical form which can overcome these drawbacks without at the same time
20 controlling release of the active ingredient constitutes a good solution to the problem.

An object of the present invention is therefore to produce formulations in extemporaneous suspension, in particular for oral use, which, while allowing prompt release of the active ingredient, at the same time avoids those aforementioned problems that can be encountered with common ready-to-use suspensions.

25 In addition, the present coated nuclei, preferably the coated microgranules, can be formed into tablets or solid aggregates obtained for instance by lyophilizing a mixture of coated nuclei and of a vehicle of excipients, that can be administered without water. Thus there is no need of reconstitution by admixing them with a liquid phase before administration. The patient itself provides the fluid, e.g., saliva.

30 **SUMMARY**

The present invention is represented by a prompt-release pharmaceutical composition comprising:

a) a plurality of nuclei having dimensions between 50 and 500 µm, selected among microcrystals of the active ingredient and microgranules containing at least one

active ingredient and at least one pharmaceutically acceptable excipient;
b) a lipidic coating comprising a lipidic material sprayed in the melted state onto the said nuclei, and optionally at least one hydrophilic additive;
c) a vehicle comprising one or more pharmaceutically acceptable excipients.

5 Other aspects of the present invention are represented by the the coated nuclei, and by the the process of preparation of the present compositions and/or coated nuclei. Other objects of the present inventions will be apparent from the present description text.

It has been found in this context that by applying lipid materials in the melted state by
10 film-coating, optionally in the presence of hydrophilic additives which act as wetting elements, it is possible to obtain formulations suitable for extemporaneous suspension and capable of masking the taste of the active ingredient and improving its stability characteristics.

In particular, the present invention comprises coating microgranules or crystals of
15 active ingredient, having dimensions between 50 and 500 µm and preferably between 100 and 300 µm, with lipid material in the melted state, such that the coated micronuclei can form a suspension which can be reconstituted by the patient immediately before use by simply adding the suspending phase, or formed into tables or solid aggregates.

20 The suspension, reconstituted at the time of use by admixing the coated nuclei and the vehicle with optionally the liquid suspending phase, is designed to allow release of the active ingredient only a few minutes after ingestion. It is thus possible to have in suspension mixtures of different active ingredients, even those chemically incompatible with one another, and to have preparations with good flavor masking,
25 but without release of the active ingredient being substantially influenced by the formulation. Specifically, such release occurs within a time from reconstitution not exceeding 60', depending on the greater or lesser solubility of the active ingredient in the suspending phase.

By means of the invention, the assimilation conditions of the suspension thus mimic
30 the ingestion conditions of a film-coated tablet which normally requires a time varying from 30 to 60' before the active ingredient can be solubilized and absorbed. The average percentage dissolution of a tablet is estimated by many pharmacopeias to be equal to 75% within a period of 45' [U.S. Pharmacopeia XXIII, p. 1925].

It is obvious that a liquid containing the active ingredient in the form of granules of reduced dimensions, coated with lipid material, is easier to swallow as compared to a tablet.

PRIOR ART

- 5 The use of waxes to coat tablets, to mix with powders, or for preparing drug/melted wax granulates, has been known for some time in the prior art.

Waxy materials have been used to form waxy matrices of tablets or granulated materials, principally for the purpose of obtaining controlled-release formulations [Pharm. Acta Helv., 56 4/5, 111 (1981)].

- 10 US Patent 4,764,375 describes the possibility of obtaining crystals of soluble active ingredients that are directly incorporated into melted waxes, and the possibility of forming extemporaneous suspensions with or without the addition of surfactants.

Patent application EP 608,850 discloses how to form microgranulated materials having characteristics such that they can easily be suspended in aqueous solutions after film-coating.

- 15 **DETAILED DESCRIPTION OF THE INVENTION**
- The present invention typically applies to active ingredients endowed with palatability and/or taste problems, with poor stability in the administration vehicle, or with hygroscopicity problems, such as the drugs hereinabove mentioned in the present application.

Other examples of active ingredients which may be included in the coated nuclei suitable for use according to the present invention are diphenylhydramine hydrochloride or citrate, prednisone, fluoxetine, fluconazole, paroxetine, ketoprofen, dextromethorphan hydrobromide.

- 20 Typically, the nuclei to be coated according to the present invention are microgranules, and they are preferably obtained by wet granulating one or more active ingredients with one or more pharmaceutically acceptable excipients.

Suitable excipients are for instance binders, fillers, lubricants, aromatizing agents, buffering agents, antioxidants agents and mixtures thereof.

- 25 For instance, the binder can be polyvinylpyrrolidone, polyvinylpyrrolidone/vinyl acetate copolymer, cellulose derivatives (esters, ethers), and mixture thereof; the fillers can be dibasic calcium phosphate, lactose, microcrystalline cellulose, starch, sugars, or mixtures thereof; the lubricants can be talc or magnesium stearate; the buffering agents can be citric acid and tartaric acid.

The fluids typically used for granulating the active ingredients with the excipients, hereinafter referred to as binding or granulating fluids, can be water or organic solvents, such as ethyl alcohol or other commonly used solvents, or any mixture thereof.

- 5 According to a typical embodiment of the present invention, the nuclei to be coated are microgranules obtained by wet granulating the active ingredient with a mixture of a filler, such as lactose, and of a binder, such as polyvinylpirrolidone, and optionally also of a plasticizing agent, such as for instance polyethyleneglycole. The granulating fluid is typically water.
- 10 Preferably, the microgranules to be coated according to the present invention are wet granulated in a high-shear mixer-granulator equipped with a mixer and a mill, wherein the mixture of the active ingredients and of the excipients is wetted with a binding fluid then kneaded, wetting and kneading being both carried out under the combined action of the mixer and of the mill. The amount of binding fluid can be for instance of about 20-50 grams per kilogram of dry mixture of active ingredients and of excipients.
- 15

In the present text, dryness levels typically correspond to a residual water content lower than about 10% by weight, preferably lower than about 5%-8% by weight.

- 20 The various active ingredients that can be used according to the present invention are preferably converted into microgranular nuclei specifically according to the procedure described by application EP 608,850, which is herein incorporated by reference. For the purposes of the invention, it is extremely important to have available microgranulated materials with morphological characteristics suitable both for subsequent coating and for producing a good suspension.

- 25 To prevent the lipid material applied onto the nuclei from exerting an excessive delaying effect on release of the active ingredient, it is therefore spray-deposited onto the microgranulated material itself in layers of greater or lesser thinness depending on the differing solubility of the active ingredient.

- 30 Preferably, the lipiddic coating according to the present invention is in amounts such as to not substantially affect the final dimensions of the particles to be coated, which preferably remain within the size ranges hereinafter reported for the nuclei to be coated.

In theory, if the active ingredient is present in homogeneous form, with crystals of regular shape with no sharp angles, the lipid material could be applied directly onto

the crystals of active ingredient. It is obvious, however, that this kind of situation, although not impossible, is quite specific and may be encountered only in a very limited number of cases.

This problem can be overcome, however, in the case of the present invention, since

- 5 it will always be possible to resort to microgranulation of the active ingredient in order to make the coating process applicable to any active ingredient regardless of its crystalline and morphological characteristics.

In principle, various techniques can be used for coating nuclei. Some of these, however, exhibit limitations that make industrial use impractical.

- 10 The possibility is thus known, for example, of performing coatings in rotating tanks. This technology cannot, however, be applied successfully to the coating of microgranulated materials having dimensions between 100 and 300 um, due to problems of agglomeration between the particles being coated.

- 15 The microencapsulation technology, on the other hand, which has already been successfully applied for direct coating of active ingredients (U.S. Patent 4,822,619), requires the use of solvents and is difficult and complex to standardize.

- It has been found that in the case of the present invention, the most suitable technology consists in coating the nuclei, preferably the aforementioned microgranules in fluidized-bed equipment by means of the Wurster^R system [Pharm. 20 Res 7 (11), 1119 (1990)].

- In this system, the lipidic coating material is sprayed in melted state through a nozzle onto the particles which are held suspended by a stream of air inside a cylinder. After exposure to the coating material, the particles have the opportunity to decelerate in an expansion chamber, and to drop to the bottom of the device to begin a new film-coating cycle.

- Among the various materials appropriate for coating, lipid materials are those found to be most suitable for achieving the goal of obtaining coated particles such that release of the active ingredient begins predominantly after 1 minute (preferably, no more than 10% by weight of the active ingredient is released within 1 minute from 30 reconstitution of the liquid suspension or from ingestion of the tablets or solid aggregates), and is predominantly complete within 45 minutes (preferably, at least 75% by weight of the active ingredient is released within 45 minutes from reconstitution of the liquid suspension or from ingestion of the tablets or solid aggregates).

It is moreover known that lipid materials, in addition to being hydrophobic, are poorly soluble in most common organic solvents usable in the pharmaceutical field. Optimum solvents would thus be the chlorinated ones, such as chloroform, dichloroethane, carbon tetrachloride, and the like, although they have considerable limitations as far as toxicological and environmental aspects are concerned.

5 It has therefore been found, and is a part of the present invention, that by adapting so-called melted-wax technology to said materials, it is possible to apply a layer of lipid material onto the nuclei in a controlled manner the lipidic material being atomized in the melted state, using only preheated compressed air as the atomization fluid. In this manner the lipid materials, which are kept molten, are 10 atomized in the desired quantity, without the aid of any solvent, onto the nuclei containing the active ingredient.

According to a typical embodiment of the present invention, the lipidic material is 15 preferably melted at a temperature of about 40°C-60°C above its melting point, then sprayed onto the nuclei at a temperature preferably of about 20°C-30°C above its melting point, at a spraying rate of preferably 2.0-4.0 grams/minute, more preferably of 2.5-3.5 grams/minute.

Compressed air used as the atomization fluid is preheated, typically at a temperature 20 of about 40°- 60°C above the melting point of the selected lipidic material, and atomized at a pressure preferably of about 2.5-3.5 bars, typically of about 3 bars.

Coated microgranules are then cooled, preferably to about 10-15°C below the melting point of the lipidic material, for not less than 10 minutes, and then further cooled till they reach the room temperature (25-30°C).

Lipid materials suitable for the purpose, usable alone or mixed, are:

- 25 - Mono-, di-, and triglycerides of fatty acids having from 6 to 32, preferably from 12 to 22, typically 16 or 18 carbon atoms, principally saturated, such as: Monostearin, dipalmitin, tristearin, hydrogenated castor oil (Sterotex) (R);
- Fatty acids or fatty alcohols having from 6 to 32, preferably from 12 to 22, typically of 16 or 18 carbon atoms, such as: stearic acid, cetyl alcohol, stearyl alcohol;
- 30 - Esters of propylene glycol or of sucrose with fatty acids having from 6 to 32, preferably from 12 to 22, typically of 16 or 18 carbon atoms, such as: propylene glycol monostearate, sucrose monostearate, and sucrose monopalmitate;

- Waxes, such as: beeswax white wax (a refining product obtained by treating with oxidizing agents natural, yellow beeswax), candelilla wax, carnauba wax, and the like.

Typically, the amount of lipidic material applied to the nuclei is of about 1%-25% by weight, and preferably of about 5%-20% by weight, with respect to the weight of dry nuclei (microcrystals or microgranules) to be coated (dryness levels being preferably as hereinabove reported in the present text for microgranules).

It has also been found, and this also forms part of the present invention, that the wettability of the present coated microgranules is further improved by adding a hydrophilic additive to the lipidic coating, thus further reducing tendency of suspended particles, if any, to float and/or to adhere to the walls of the reconstitution container.

Suitable hydrophilic materials are the hydrophilic polymers, in particular: water soluble polymers, for instance semisynthetic ones, such as cellulose derivatives (ethers, esters) such as: cellulose acetophthalate, hydroxypropylmethylcellulose [Methocel®], hydroxyethylcellulose, hydroxypropylcellulose, or synthetic polymers such as, polyethylene glycol, and the like. It is important in any case to apply the polymer in quantities such as not to create gastroresistance or release control beyond the desired limits. This quantity of hydrophilic element may lie in the range between 0.1% and 5%, preferably between 0.5 and 2%, by weight of hydrophilic component with respect to the lipid coating material.

The hydrophilic additive can be either incorporated into the lipidic layer deposited onto the nuclei (e.g. by dispersing the hydrophilic additive into the melted lipidic material, prior to spraying it onto the nuclei), or applied as separate layer onto the lipidic layer (e.g. by spraying a solution thereof in appropriate solvent onto the nuclei already coated with a lipidic layer).

Other examples of hydrophilic additives suitable for the purpose are ionic surfactants for instance anionic surfactants, among them those containing carboxylate, sulfonate, or sulfate groups such as dioctyl sodium sulfosuccinate or sodium lauryl sulfate, or nonionic surfactants such as partial esters of fatty acids with anhydrides of sorbitol (Span) or with polyoxyethylene ethers of fatty acid partial esters of sorbitol anhydrides (Tween).

Fatty acids have from 6 to 32, preferably from 12 to 22, and typically 16 or 18 carbon atoms.

The lipidic coating according to the present invention achieves the goals of providing sufficient masking effect of unpleasant taste and/or protective effect towards degradation of active ingredient, and a satisfactory release pattern of the active ingredient, using amounts of lipidic material sufficiently low to allow the dimensions of the coated nuclei to be preferably maintained within the prescribed limits hereinabove reported, and to be applied onto the nuclei in a uniform manner, so to produce coated nuclei as smooth as possible, suitable for suspensions in liquid medium.

According to a preferred embodiment of the present invention, the lipidic material to be applied to the nuclei comprises at least one mono-glyceride or di-glyceride of a fatty acid (preferably a mono-glyceride, such as glyceryl monostearate) and at least one wax (such as beeswax, white wax or candellilla wax); more preferably, such lipidic material also comprises at least one fatty alcohol, such as cetyl alcohol, stearyl alcohol, or mixtures thereof, typically a mixture of cetyllic and stearyl alcohol.

In particular, a typical lipidic coating according to the present invention contains, with respect to the total weight of lipidic material: about 40%-95% by weight, typically about 80%-90% by weight, of a mono-glyceride or di-glyceride of fatty acids, preferably of a mono-glyceride of fatty acids; about 5%-50% by weight, typically about 5%-20% by weight, and more preferably about 5%-10% by weight, of a wax; preferably, such lipid mixture may optionally further comprise about 0.5%-5% by weight, typically 1%-3% by weight of one or more fatty alcohols; typically the amount of such lipidic coating is of about 10% by weight with respect to the nuclei to be coated.

For instance, a preferred lipidic coating according to the present invention may contain about 90% by weight of glyceryl monostearate, about 8% of a wax, about 1% by weight of cetyl alcohol, and about 1% by weight of stearyl alcohol.

According to a further preferred embodiment of the present invention, the lipidic material used to coat the nuclei further comprises 1%-3% by weight of a hydrophilic polymer, such as hydroxypropylmethyl cellulose, or 2%-3% by weight of a surfactant, such as dioctyl sodium sulfosuccinate or sodium lauryl sulfate (percentages being referred to the total amount of lipidic coating).

According to another embodiment of the present invention, the lipidic coating comprises at least one trygliceride, such as hydrogenated castor oil, and preferably it also contains about 0.5%-2% by weight of an hydrophilic additive, such as

polyethylene glycole, percentages being referred to the total amount of lipidic material.

Typically, the lipidic mixture is melted at about 110°C-130°C, then sprayed onto the nuclei to be coated at about 80°C, at a spraying rate preferably of about 2.5-3.2
5 grams/minute, using compressed air preheated preferably at about 110°C-130°C, with a pressure preferably of about 3 bars.

Once coated in this manner, the microgranulated material containing the active ingredient can be further formulated with the addition of one or more other excipients which represent the "vehicle," which will then be reconstituted with the external
10 phase prior to use in a suitable container.

The vehicle can be either admixed with the coated nuclei, and stored in dosage forms, or added to the liquid suspending phase. In the former case, such vehicle of excipients is typically in solid form, and it does not allow any substantial release of the active ingredient in it. If desired, the mixture of the coated nuclei with the vehicle
15 can be lyophilized, so to ensure the active ingredient to be stored in a sufficiently dry form.

The constituents of the vehicle can be selected among the following ones and any mixture thereof:

- Suspending or structuring agents such as: cellulose esters, microcrystalline cellulose, alginic acid derivatives, polyvinylpyrrolidone or derivatives;
- Sugars, which represent the substrate of the said vehicle, such as: sucrose, sorbitol, xylitol, dextrose, mannitol, and the like;
- Buffering substances such as: citric acid, sodium citrate, sodium phosphate and potassium phosphate, and the like;
- 25 - Flavors and edulcorants such as: saccharine, aspartame, and flavors commonly used in the pharmaceutical sector.

Substances to reinforce the taste, such as citric acid, sodium chloride, and the like, can also be present.

Types and amounts of excipients constituting the vehicle, either in the case of
30 suspensions, or of tablets or solid aggregates, may vary as a function of the type and solubility of the active ingredient, the vehicle being typically in weight amounts of from 5 to 10 times the weight of the coated nuclei.

Typically, the vehicle comprises a sugar (e.g. sucrose, optionally in admixture with mannitol), generally admixed with a suspending or structuring agent (such as

polyvinylpirrolidone), and optionally with other excipients, such as flavoring agent (such as lemon flavour), a buffering substance (such as citric acid), and other excipients such as precipitated silica.

According to a typical embodiment, such vehicle contains about 80%-98% by weight

5 of one or more sugars (typically a mixture of sucrose and of mannitol, in weight ratios of about 8:1 to 5:1) and about 1%-2% by weight of a structuring agent (for instance polyvinylpirrolidone); optionally, such vehicle may also contain about 1%-2% by weight of a flavoring agent, about 2%-4% by weight of a buffering substance, and about 0.1%-0.2% of silica gel.

10 Before being reconstituted with the appropriate external phase by the patient, the mixture intended for suspension, represented by the coated nuclei, optionally admixed with said vehicle can be distributed into various dosage forms.

Particularly convenient is the single-dose packet, generally consisting of a paper/aluminum/polyethylene laminate. Laminates having 10 g/m² paper, aluminum at a thickness of 10 to 20 um, and 30 g/m² polyethylene can be used for packets.

15 Another single-dose dosage form consists of reservoir-stopper vials. They have the advantage that the vehicle is already present in them in the liquid phase contained in the bottle, while the coated nuclei (preferably said microgranules) are stored in the reservoir stopper. The user, having removed a protective ring, can breach the
20 reservoir stopper by pressing on it, causing the microgranules to drop into the part below containing the liquid vehicle.

For administrations which require multiple doses, a dosage form can be used comprising a multi-dose bottle containing a mixture of coated nuclei (preferably said microgranules) and the vehicle. The user can measure out this mixture using

25 appropriate solid measures, thus reconstituting the necessary quantity of suspension.

A mixture of several active ingredients can be present simultaneously in the same dosage form.

The pharmaceutical composition according to the present invention allows the
30 quantity of the various components of the mixture of active ingredients present in the same dosage unit to be modulated as a function of a specific, personalized therapeutic treatment.

The external phase used as suspending medium is typically an aqueous phase, and may be either added by the user (e.g. potable water used by the patient to dissolve

the drug), or included in the pharmaceutical composition, e.g. a suspending phase which may contain one or more excipients, including those hereinabove mentioned for the vehicle.

In addition, the coated nuclei, preferably the coated microgranules, can be formed
5 into dosage unit forms such as tablets or solid aggregates, typically lyophilized, and
the like. These can be administered without water or the need for reconstitution. The
patient itself provides the fluids (saliva or gastrointestinal fluids). The ingredients
usually employed in the preparation of the tablets include excipient materials like
those described above and also include: mannitol, dextrins, sugars, etc. as diluents
10 in presence of binders such as, for example, gelatin or polyvinylpyrrolidone (PVP),
and the like. Flavoring agents and edulcorants can also be added to these materials.
It has also been found that the inclusion of an effervescent mixture in the lyophilized
tablet or solid aggregates is particularly useful in further reducing the sand effect of
15 the microparticles. Materials suitable for preparing an effervescent mixture are
bicarbonates and organic acids such as citric acid or tartaric acid and the like. The
effervescent tablets or solid aggregates are then lyophilized in presence of organic
solvents, such as: dioxane, terbutyl alcohol, etc.

An assessment of the release time of the active ingredient of the formulation was
made by dispersing the microgranulated material, coated with lipid material, in water,
20 then taking a sample of the solution at different times and determining the amount of
active ingredient contained in it. The microgranulated material had to be coated with
lipid material in such a way that during the time needed to reconstitute it with water
(approximately a minute) there was no release of active ingredient, and that release
was complete after 45 minutes, in order to avoid slow-release phenomena which are
25 not within the context of the present invention.

Several examples are supplied below, with the sole purpose of better illustrating the
invention in question by demonstrating its advantages and applicability, but without
constituting any limitation thereof.

30 EXAMPLE 1

Microgranular formulation of potassium bicarbonate

2 kg of potassium bicarbonate was mixed with lactose and polyvinylpyrrolidone K 30,
and wetted with 100 ml of water in a Fielder P25 granulator. After adding the water
and granulating for 10', the granulated material was dried and sieved until a granule

fraction was obtained having dimensions between 100 µm and 300 µm. A mixture of lipids having the following composition was then applied onto the granulated material:

5	Component	% (w/w)
	Beeswax	8
	Glyceryl monostearate	90
	Cetyl alcohol	1
	Stearyl alcohol	1

10

The lipids were first melted at a temperature of approximately 110°C, and then sprayed in the melted state, with the temperature maintained at approximately 80°C, using compressed air preheated to a temperature of 125°C and at a pressure of 3 bar. The spraying process is performed with a 7" Wurster insert on a Glatt GPCG 3 apparatus. The quantity of lipid material was equal to 15% w/w with respect to the granulated material, and it was sprayed at a rate of 2.5 g/min. In the final phase of the coating process, sodium lauryl sulfate in a quantity equal to 1% of the weight of the lipids used was dispersed in the melted lipids. The microgranulated material coated in this manner exhibited good dispersibility in water.

20

EXAMPLE 2

Tasteless, prompt-release microgranular compositions of diltiazem

Using the method described in Example 1, a microgranulated material having the following composition was prepared:

25

Component	Weight (g)
Micronized diltiazem hydrochloride	600
Micronized lactose (Microtose (R))	2100
Polyvinylpyrrolidone K30	300

30

After drying, the fraction of granules having dimensions between 125 and 300 µm was separated by sieving. A Glatt GPCG 3 apparatus with a 7" Wurster insert and 1.2 mm nozzle was used to apply a composition consisting of the same mixture of components in two different formulations (I and II):

Component	Formula I	Formula II (%)
Glyceryl monostearate	90	49
White wax	8	49
5 Cetyl alcohol	1	1
Stearyl alcohol	1	1

The lipid components were melted at a temperature greater than 80°C, and were then sprayed with a pump having a flow rate of 3.2 g/minute and an atomization pressure of 3 bar, using compressed air preheated to a temperature of 120°C.

10 The following nine different coating tests (A-I) were performed; indicated for each is the percentage of coating material and the respective percentage of surfactant (dioctyl sodium sulfosuccinate - DSS) used, where applicable.

	A	B	C	D	
15 Formula I	10%	15%	20%	20%	
DSS	-	-	-	0.2%	
	E	F	G	H	I
20 Formula II	5%	10%	15%	20%	20%
DSS	-	-	-	-	0.2%

In formulations D and I, the percentage of surfactant was calculated with respect to the waxes and was added at the end, incorporating it directly into the lipid material.

25

EXAMPLE 3

Dissolution tests on formulations containing diltiazem

The dissolution of formulations (A-I) of Example 2 was determined in accordance with the procedure cited in USP XXIII, p. 1787, using 900 ml of distilled water, and 30 spectrophotometric reading at a wavelength of 240 nm. 1 ml of solution was taken respectively at 1', 30', and 45' from the beginning of the test. Table I below lists percentage values of diltiazem detected in solution for each of the formulations analyzed.

TABLE I

		% diltiazem released								
	Time	A	B	C	D	E	F	G	H	I
5	1'	3.2	0.2	0	2	26	2.7	2	0.3	2
	30'	100	91	93	98	100	75	36	15	83
	45'	100	100	95	99	100	98	78	52	100

EXAMPLE 4

10 Preparation of single-dose packets of prompt-release diltiazem

3.45 kg of granular phase, coated according to formulation B of Examples 2 and 3, was mixed with a vehicle consisting of:

	Component	Weight (kg)
15	Mannitol	5
	Polyvinylpyrrolidone	0.5
	Lemon flavor	0.5
	Citric acid	0.9
	Precipitated silica	0.05
20	Sucrose to make	30

The resulting mixture was measured into 10,000 3-gram packets each containing 60 mg of diltiazem hydrochloride, using a Marchesini packing machine. The composition of each packet was 30 g/m² paper, 12 µm aluminum, and 40 g/m² polyethylene.

25

EXAMPLE 5

Microgranulating acetaminophen and coating to mask taste

The method described in Example 1 was used to prepare a microgranulated material having the following composition: 50% acetaminophen, 40% lactose, 10% 30 polyvinylpyrrolidone (PVP K30). After granulation with water, drying, and sieving over a 0.6 mm mesh to separate the fraction between 100 and 300 µm, the resulting granulated material was coated under the conditions stipulated by Example 2 with a lipid mixture containing 80% glyceryl monostearate and 20% carnauba wax. The coated granulated material was mixed with a vehicle in such a way that after

distribution into packets, each packet had the following composition:

Component	Weight (g)
Granulated acetaminophen	0.550 (equal to 0.250 g of acetaminophen)
5 Polysorbate 80	0.01
E 110 coloring	0.0016
Citric acid	0.1
Orange flavor	0.10
Orange powder	0.60
10 Caraway flavor	0.003
Precipitated silica	0.01
Powdered sugar to make	3

The polysorbate 80 was absorbed onto the precipitated silica before being mixed
15 with the other excipients of the packet.

EXAMPLE 6

Prompt-release suspension of naproxen with taste masking

The method described in Example 1 was used to prepare a microgranulated material
20 having the following composition: 3200 g micronized naproxen, 400 g polyvinylpyrrolidone (PVP K30), 400 g lactose, and 30 g polyethylene glycol (PEG 6000). After mixing for 5 minutes, 500 ml of water was added by spraying at 2 bar with agitation, and the mixture was mixed for another 15 minutes until the microgranules formed and spheroidized. Drying was performed for 2 hours at 35°C in
25 a static oven to a residual moisture of between 4 and 5% by weight, and a 0.6 mm sieve was used to separate the fraction of microgranules between 90 and 300 µm. A lipid mixture having the following composition (Formula III) was applied to the resulting granulated material:

30 Glyceryl monostearate	90%
Beeswax	8%
Cetyl alcohol	1%
Stearyl alcohol	1%

The following six different coating tests (L-P) were performed, for which an indication is given of the percentage of coating material and the respective percentage of surfactant (Methocel (R) E15LV) added where applicable. In the case of formulations 5 N, O, and P, the Methocel (R) was sprayed after having been dissolved in an 80:20 mixture of methanol and water.

	L	M	N	O	P	Q
Formula III	5%	10%	10%	10%	10%	15%
10 Methocel (R) E15LV	-	-	1%	2%	3%	-

EXAMPLE 7

Dissolution tests for the formulations containing naproxen

Dissolution of the formulations L-Q was performed according to the method indicated 15 in Example 3, using a pH 7.4 phosphate buffer as the medium and reading the spectrophotometric absorption at 330 nm. The results are indicated in Table II below.

TABLE II

20	Time	% naproxen released					
		L	M	N	O	P	Q
	1'	0.3	0.2	0.2	0.5	0.5	0.5
	30'	56	29	40	48	50	22
	45'	75	55	63	80	85	40

25 EXAMPLE 8

Prompt-release suspension of ibuprofen with taste masking, for pediatric use

A mixture consisting of 400 g of micronized ibuprofen, 500 g of lactose, and 100 g of polyvinylpyrrolidone was mixed for 5 minutes and granulated with 210 ml water for 20 minutes. The mixture was then dried at 40°C in a fluidized bed for 10 minutes to a 30 residual relative moisture of approximately 5% by weight. The fraction between 100 and 300 µm was separated, and a lipid composition (7.5% by weight with respect to the granulated material) was applied consisting of hydrogenated castor oil (Sterotex®) to which 1% polyethylene glycol (PEG 6000) had been added in the final film-coating phase. The microgranulated material coated in this manner was

measured into the reservoir stopper of single-dose vials having as vehicle an 8-ml solution having the following composition:

	Sorbitol	3500 mg
5	Avicel	50 mg
	Orange flavor	50 mg
	Citric acid	15 mg
	Sodium benzoate	10 mg
	Water to make	8 ml

10

Before use, the microgranular contents of the reservoir stopper (equal to 100 mg ibuprofen) were brought into contact with the liquid in the vial, and after agitation could be taken by the patient.

15 EXAMPLE 9

Extemporaneous suspension of moguisteine with taste masking

- A mixture consisting of 49% moguisteine, 10% polyvinylpyrrolidone (PVP K30), 40% lactose, was mixed in a Fielder P25 kneader/granulator. A 5% aqueous solution of polyethylene glycol (PEG 6000), in amount corresponding to a PEG content of 1% by weight with respect to the total mixture as above defined, was added to the mixture at a rate of 25 ml/min, using a 0.8 mm nozzle and a spray pressure of 2 bar. Kneading proceeded for approximately 20' at a speed of 200 rpm, then the granulated material was allowed to spheroidize for another 15'. After drying, the granulated material was separated by sieving, yielding a fraction with dimensions between 100 and 300 µm. The microgranulated material was then coated with a lipid mixture having the following composition:

	Glyceryl monostearate	90%
	Beeswax	8%
30	Cetyl alcohol	1%
	Stearyl alcohol	1%

1% by weight (with respect to the mixture) dioctyl sodium sulfosuccinate was added to this mixture in the final spraying phase by dispersion into the melted mass. The

weight of the coating mixture was 5% of the weight of the microgranulated material being coated. The coated microgranulated material was then mixed with a vehicle such that after distribution into packets, each packet had the following composition:

	Component	Weight (mg)
5	Granular mogusteine	430 (equal to 200 mg mogusteine)
	Avicel (R) RC 591	500
	Ammonium glycyrrhizinate	50
	Fruit flavor	50
10	Sucrose to make	3000

EXAMPLE 10

Lyophilized tablet

Tablet having the following composition: coated granules placebo 50 mg, a vehicle containing the following excipients: gelatin 40 mg, mannitol 30 mg, aspartame 0.5 mg, citric acid 3.5 mg and also water 480 mg are prepared as follows: the gelatin is dissolved in water heated at 60°C. Mannitol, citric acid and aspartame are added until solubilization is complete. The coated granules are added until an homogeneous suspension is obtained. The mixture is placed in blister pockets with 12 wells with a 6 mm diameter at the weight of 600 mg. Lyophilization is performed by freezing at about -40°C to about -45°C for 2-3 hours, then gradually raising the temperature up to about 25°C under a vacuum of about 0.2-0.25 mbar. After lyophilization is completed, the blister is sealed with an aluminium foil.

EXAMPLE 11

Effervescent tablet

Following the method described in Example 10, a formulation having the following composition is prepared:

naproxen coated granules (prepared in Example 6) 357 mg, sodium bicarbonate 52 mg, lactose 103.5 mg, saccarose 155 mg, ascorbic acid 52 mg, sodium sacchararinate 2.64 mg, flavour 12 mg, PVP K 30 65.86 mg and terbutyl alcohol 800 mg.

The sodium bicarbonate, lactose, saccarose, ascorbic acid and sodium saccharinate are sieved to obtain particles having dimensions of about 100 µm. The components

are added to PVP solubilized in t-butyl alcohol. The coated microgranules of naproxen are suspended in the mixture. The mixture is then suspended in blister packets and lyophilized as described in Example 10.

CLAIMS

1. Prompt-release pharmaceutical composition for administration of an active ingredient, said composition comprising:
 - a) a plurality of nuclei having dimensions between 50 and 500 µm, selected among microcrystals of the active ingredient and microgranules containing at least one active ingredient and at least one pharmaceutically acceptable excipient;
 - b) a lipidic coating comprising a lipidic material sprayed in the melted state onto the said nuclei, and optionally at least one hydrophilic additive;
 - c) a vehicle comprising one or more pharmaceutically acceptable excipients.
2. The pharmaceutical composition according to claim 1, for oral use.
3. The pharmaceutical composition according to claim 1, characterized in that said nuclei are microgranules containing at least one active ingredient and at least one pharmaceutically acceptable excipient.
4. The pharmaceutical composition according to claim 1, characterized in that no more than 10% by weight of the active ingredient is released within 1 minute from reconstitution of the composition; and that at least 75% by weight of the active ingredient is released within 45 minutes from reconstitution of the composition.
5. The pharmaceutical composition according to claim 1, characterized in that the lipidic material is selected among: mono-, di- or tri- glycerides of fatty acids having from 6 to 32 carbon atoms, fatty acids having from 6 to 32 carbon atoms, fatty alcohols having from 6 to 32 carbon atoms, esters of propylene glycols or of sucrose with fatty acids having from 6 to 32 carbon atoms, waxes, and mixtures thereof.
6. The pharmaceutical composition according to claim 5, characterized in that the lipidic material is selected among monostearin, dipalmitin, tristearin, hydrogenated castor oil, stearic acid, cetyl alcohol, stearyl alcohol, propylene glycol monostearate, sucrose monostearate, sucrose monopalmitate, beeswax, white wax, candelilla wax, carnauba wax, and mixtures thereof.
7. The pharmaceutical composition according to claim 1, characterized in that the amount of lipidic material applied onto the nuclei is of 1%-25% by weight with respect to the weight of the nuclei to be coated.
8. The pharmaceutical composition according to claim 1, characterized in that the hydrophilic additive is selected among hydrophilic polymers and surfactant agents.
9. The pharmaceutical composition according to claim 8, characterized in that the

2 hydrophilic additive is incorporated into the lipidic layer deposited onto the nuclei, or
3 applied as a separate layer onto the lipidic layer.

1 10. The pharmaceutical composition according to claim 8, characterized in that
2 hydrophilic polymers are selected among cellulose acetophthalate,
3 hydroxypropylmethylcellulose and polyethylene glycole, and surfactants are selected
4 among dioctyl sodium sulfosuccinate, sodium laurylsulfate, partial esters between
5 C₆-C₃₂ fatty acids and anhydrides of sorbitol, and polyethylene ethers of C₆-C₃₂
6 fatty acids partial esters of sorbitol anhydrides.

1 11. The pharmaceutical composition according to claim 1, characterized in that the
2 amount of hydrophilic additive is of 0.1%-5% by weight, with respect to the amount of
3 lipidic material.

1 12. The pharmaceutical composition according to claim 1, characterized in that the
2 lipidic material is a mixture comprising at least one mono-glyceride or di-glyceride of
3 a fatty acid, at least one wax, and optionally at least one fatty alcohol.

1 13. The pharmaceutical composition according to claim 12, characterized in that the
2 lipidic material comprises 40%-95% by weight of at least one mono- glyceride or di-
3 glyceride of fatty acids, 5%-50% by weight of at least one wax, and optionally 0.5%-
4 5% of at least a fatty alcohol, the percentages being referred to the total amount of
5 lipidic mixture.

1 14. The pharmaceutical composition according to claim 12 or 13, characterized in
2 that the mono-glyceride is glyceryl monostearate, the wax is selected among
3 beeswax, white wax and carnauba wax; the fatty alcohol is selected among cetyl
4 alcohol, stearyl alcohol and mixtures thereof.

1 15. The pharmaceutical composition according to claim 12 or 13, characterized in
2 that the lipidic material further comprises 1%-3% by weight of a hydrophilic polymer,
3 or 2%-3% by weight of a surfactant.

1 16. The pharmaceutical composition according to claim 1, characterized in that the
2 lipidic material comprises at least one triglyceride, and optionally about 0.5%-2% of a
3 hydrophilic additive.

1 17. The pharmaceutical composition according to claim 16, characterized in that the
2 triglyceride is hydrogenated castor oil, and the additive is polyethylene glycole.

1 18. The pharmaceutical composition according to claim 1, characterized in that said
2 nuclei are microgranules with a mean geometric diameter of 120-200 µm, with a

- 3 standard deviation of 1.4-2.0, an aerated density of 0.4-0.7 g/ml, a packed density of
4 0.5-0.9 g/ml, an apparent density of 1.2-1.5 g/ml, a Carr Index of 5%-15%, and an
5 angle of repose of 20°-40°.
- 1 19. The pharmaceutical composition according to claim 1, characterized in that nuclei
2 are microgranules containing the active ingredient and a mixture of a filler and of a
3 binder, and optionally also a plasticizing agent.
- 1 20. The pharmaceutically composition according to claim 19, characterized in that
2 the filler is lactose, the binder is polyvinylpirrolidone, the plasticizing agent is
3 polyethylene glycole.
- 1 21. The pharmaceutical composition according to claim 1, characterized in that the
2 active ingredient is selected among those having unpleasant palatability or taste,
3 poor stability in the administration vehicle, or hygroscopicity.
- 1 22. The pharmaceutical composition according to claim 1, characterized in that the
2 active ingredient is selected among acetaminophen, naproxen, ibuprofen, diltiazem,
3 moguisteine, potassium bicarbonate, diphenylhydramine hydrochloride or citrate,
4 prednisone, fluoxetine, fluconazole, paroxetine, ketoprofen and dextromethorphan
5 hydrobromide.
- 1 23. The pharmaceutical composition according to claim 1, characterized in that the
2 vehicle comprises at least one excipient selected among suspending or structuring
3 agents, sugars, buffering substances, flavors, edulcorants, substances to reinforce
4 the taste, and any mixture thereof.
- 1 24. The pharmaceutical composition according to claim 1, characterized in that it
2 further comprises an external phase comprising an aqueous phase, optionally added
3 with one or more excipients.
- 1 25. Pharmaceutical composition according to claim 1, suitable for use in the
2 preparation of an extemporaneous suspension.
- 1 26. Dosage unit form comprising a pharmaceutical composition according to claim 1,
2 characterized in that it is a tablet or a solid aggregate.
- 1 27. Dosage unit form according to claim 26, characterized in that it is an effervescent
2 tablet or solid aggregate.
- 1 28. A process for the preparation of a prompt-release pharmaceutical composition
2 comprising coated nuclei containing at least one active ingredient, and comprising:
3 a) a plurality of nuclei of dimensions between 50 and 500 µm, selected among

- 4 microcrystals of the active ingredient in microcrystalline form, and by microgranules
5 containing at least one active ingredient and at least one pharmaceutically
6 acceptable excipient;
- 7 b) a lipidic coating comprising a lipidic material sprayed in the melted state onto the
8 said nuclei, and optionally at least one hydrophilic additive in a minority proportion
9 with respect to the lipidic material, which comprises atomizing the melted lipidic
10 material onto the nuclei, using compressed preheated air as the atomization fluid,
11 without the aid of any solvent.
- 12 c) a vehicle comprising one or more pharmaceutically acceptable excipients.
- 1 29. The process as claimed in claim 28, characterized in that it is carried out in a
2 fluidized-bed equipment.
- 1 30. The process as claimed in claim 28, characterized in that the lipidic material is
2 melted at a temperature of 40°C-60°C above its melting point, sprayed onto the
3 nuclei at a temperature of 20°C-30°C above its melting point, with a spraying rate of
4 2.0-4.0 grams/minute, using as atomization fluid compressed air preheated at a
5 temperature of 40°C-60°C above said melting point, at a pressure of 2.5-3.5 bars.
- 1 31. The process according to claim 28, characterized in that it further comprises
2 dispersing a hydrophilic additive into the melted lipidic material.
- 1 32. The process according to claim 28, characterized in that it further comprises
2 applying a separate layer of hydrophilic material onto the lipidic layer.
- 1 33. The process according to claim 28, characterized in that it comprises preparing
2 microgranules by wetting with a fluid a mixture of at least one active ingredient with
3 one or more pharmaceutically acceptable excipients in a high-shear mixer-granulator
4 equipped with a mixer and a mill, and then kneading the mixture thus obtained, both
5 the wetting and the kneading phases being carried out the combined action of the
6 mixer and of the mill.
- 1 34. The process according to claim 33, characterized in that the fluid is used in an
2 amount of about 20-50 grams per kilogram of mixture of active ingredients and of
3 excipients to be granulated.
- 1 35. The process according to claim 33, characterized in that granulation is carried
2 out using 80-180 grams of fluid per Kg of mixture to be granulated, at a spray-rate of
3 10-40 grams/minute, at a spray-pressure of 1.5-2.5 bars, with a kneading time of 5-
4 15 minutes, using a mixer speed of 50-600 rpm, and a mill speed of 1500-4000 rpm.

- 1 36. A prompt-release pharmaceutical composition comprising coated nuclei, obtained
2 according to the process as defined in anyone of claims from 28 to 35.
- 1 37. Coated nuclei comprising nuclei and lipidic coating as defined in anyone of
2 claims from 1 to 25.
- 1 38. Use of coated nuclei comprising nuclei and lipidic coating as defined in anyone of
2 claims from 1 to 25, in the preparation of a prompt-release pharmaceutical
3 composition useful for the extemporaneous preparation of liquid suspensions, of
4 tablets or of solid aggregates.

INTERNATIONAL SEARCH REPORT

International application No.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, WPII, CLAIMS, US PAT FULL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4764375 A (GEORGE N. PARADISSIS), 16 August 1988 (16.08.88), column 1, line 64 - column 2, line 41 --	1-30,37
X	EP 0273890 A1 (ASTRA LAKEMEDEL AKTIEBOLAG), 6 July 1988 (06.07.88) --	1-38
X	US 5296236 A (GIANCARLO SANTUS ET AL), 22 March 1994 (22.03.94), column 2, line 32 - line 47; column 3, line 7 - line 38; column 3, line 53 - column 4, line 37, column 4, line 56 - line 62; column 5, line 5 - column 6, line 46; claims --	1-38

 Further documents are listed in the continuation of Box C. See patent family annex.

- * Special categories of cited documents
- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

Int'l. Search application No.

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

04/03/97

International application No.

PCT/EP 96/05127

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